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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 11/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/367,496	AGUERA ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *July 19, 2004 and October 9, 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,7,9,10,14,15,20-22,24,25,27 and 29-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *4* is/are allowed.

6)☒ Claim(s) *1,3,6,7,9,10,14,15,20-22,24,25,27 and 29-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The response filed July 19, 2004 is acknowledged and has been entered.

2. The amendment filed October 9, 2003 is acknowledged and has been entered. Claims 23, 26, and 28 have been canceled. Claims 3, 4, 9, 10, 14, 15, 20, 21, 24, 25, and 29 have been amended.

3. Claims 1, 3, 4, 6, 7, 9, 10, 14, 15, 20-22, 24, 25, 27, and 29-35 are pending in the application and are currently under prosecution.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. The following Office action contains NEW GROUNDS of rejection.

Oath/Declaration

6. The new copy of the declaration executed by Inventor Quach filed October 9, 2003 is acknowledged and has been entered.

Grounds of Objections and Rejections Withdrawn

7. Upon further consideration, in view of Applicant's amendments and arguments in the replies filed October 9, 2003 and July 19, 2004, and in favor of the new grounds of objection and rejection that follow, the grounds of rejection or objection set forth in the previous Office action mailed April 9, 2003 have been withdrawn.

Response to Arguments

8. Applicant's arguments filed October 9, 2003 with respect to the grounds of rejection set forth in the previous Office action mailed April 9, 2003 have been carefully

considered but are moot in view of the new grounds of rejection. Nevertheless, to the extent that Applicant's remarks might apply to the new grounds of rejection, Applicant's arguments have been addressed below.

Specification

9. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the peptide sequences at page 21 in lines 8-16, the peptide sequences at page 21 in lines 30 and 31, the oligonucleotide sequences at page 21 in lines 34-37, the primer sequences at page 22 in lines 36 and 37, the peptide sequence at page 27 in line 34, the polynucleotide sequence at page 35 in line 10, the probe sequences at page 39 in lines 5-7, 10, and 11, the primer sequences at page 39 in lines 34-37, the peptide sequence at page 40 in line 38, the peptide sequences at page 41 in lines 1, 3, and 5 are not identified by sequence identification numbers.

Applicant must provide appropriate amendments to the specification inserting the required sequence identifiers.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with a statement that the content of both copies are the same and, where applicable, include no new matter.

10. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of

trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of improperly demarcated trademarks include: Promega™ (page 21, line 39) and Fast Track™ (page 22, line 2).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

11. The specification is objected to because "limbic" is misspelled as "lymbic" at page 37 in line 5.

Claim Objections

12. Claims 9, 14, and 15 are objected to for the following reasons: Claim 9 is objected to because the claim recites, "useful for the diagnosis of paraneoplastic neurological syndromes and for the early diagnosis of the formation of tumors in which anti-CV2 antibodies are expressed"; claim 14 is objected to because the claim recites, "for the diagnosis of paraneoplastic neurological syndromes and for the early diagnosis of the formation of tumors in which anti-CV2 antibodies are expressed"; and claim 15 is objected to because the claim recites, "for the diagnosis in [sic] paraneoplastic neurological syndromes and for [...] the early diagnosis of the formation of tumors in which anti-CV2 antibodies are expressed". As the claims are presently constructed, the claims can be erroneously interpreted to imply that the tumors to be diagnosed using the claimed inventions express anti-CV2 antibodies; however, it is evident that the invention is disclosed as useful in diagnosing paraneoplastic neurological syndromes in which autoimmune-associated anti-CV2 antibodies are present in the serum or

cerebrospinal fluid of patients with certain tumors, not in diagnosing tumors that express anti-CV2 antibodies.

The invention is disclosed as useful in diagnosing paraneoplastic neurological syndromes, which the art defines as a collection of symptoms and clinical signs found in patients that have malignant disease; see, e.g., the definition provided by The On-Line Medical Dictionary (© Copyright 1997-2004 – The CancerWEB Project), which is published by the Dept. of Medical Oncology, University of Newcastle upon Tyne and is available on the Internet at ***http://cancerweb.ncl.ac.uk/omd/***. The On-Line Medical Dictionary discloses that, by definition, the signs and symptoms of paraneoplastic syndromes are not produced by a direct effect of a tumor or its metastases, nor due to direct invasion, compression, metastasis, infection, nutritional deficiency, or treatment of the underlying neoplasm. Rather, the paraneoplastic syndromes arise from tumor-produced biologically active proteins, autoimmunity, immune complex production, immune suppression, blockade of the normal effect of a hormone, or the release of substances from tumor-associated endothelium, which are not normally released, and finally unknown causes. Paraneoplastic neurological syndromes are those signs and symptoms of neuropathies that arise in a patient indirectly from a tumor. Thus, as disclosed, the invention provides a means for diagnosing paraneoplastic neurological syndromes in which anti-CV2 antibodies are expressed as the indirect result of a tumor; the diagnosis of such paraneoplastic neoplastic syndromes, by definition, diagnoses the tumor that is associated with the syndrome and the presence of anti-CV2 antibodies. However, the invention is not disclosed as providing a means to diagnose tumors that express anti-CV2 antibodies, as the present claim construction suggests.

This issue can be remedied by amending claims 9, 14, and 15 to recite, for example, "for the diagnosis of paraneoplastic neurological syndromes in which anti-CV2 antibodies are expressed and for the early diagnosis of the formation of tumors associated therewith". Appropriate correction is required.

13. Claims 14 and 15 are objected to because the claim 14 recites, "[...] a purified ULIP polypeptide, comprising SEQ ID No. 8, a derivative thereof, optionally attached to

a support [...]", whereas claim 15 recites, "[...] purified ULIP polypeptide comprising SEQ ID No. 8, a derivative of the ULIP optionally attached to a support [...]". In both claims, the conjunction "or", which appeared before "biologically active polypeptide fragment", was deleted by the amendment filed October 9, 2003; the claims should, for example, read, "a purified ULIP polypeptide, comprising SEQ ID No. 8, **or** a derivative thereof" (emboldened for emphasis). Amending claims 14 and 15 to insert "or" after "comprising SEQ ID No. 8," can remedy this issue. Appropriate correction is required.

14. Claim 15 is objected to because the claim recites, "for diagnosing in paraneoplastic neurological syndromes and for deleting early diagnosis of the formation of tumors". The claim should read, "for diagnosing paraneoplastic neurological syndromes", or alternatively "for diagnosis of paraneoplastic neurological syndromes", as opposed to "for diagnosing in paraneoplastic neurological syndromes". Furthermore, the inclusion of the word "deleting" is evidently a typographical error. Amending claim 15 to delete "deleting" and to recite, "for diagnosing paraneoplastic neurological syndromes", or alternatively "for diagnosis of paraneoplastic neurological syndromes" can remedy this issue. Appropriate correction is required.

15. Claim 20 is objected to because the claim recites, "selected from the group consisting of amino acid SEQ ID No. 8, a derivative or biological active polypeptide fragment thereof", which is improper Markush-type claim language. See MPEP § 2173.05(h). This issue can remedied by amending claim 20 to recite, for example, "selected from the group consisting of the polypeptide of amino acid SEQ ID NO: 8, a derivative of the polypeptide of SEQ ID NO: 8, and a biological active fragment of the polypeptide of SEQ ID NO: 8" (underlining for emphasis). Appropriate correction is required.

Claim Rejections - 35 USC § 112

16. Claims 10, 14, 15, 20, and 30-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Claims 10, 14, 15, 20, and 33-35 are directed to a genus of "derivatives" of a ULIP polypeptide comprising SEQ ID NO: 8. Furthermore, claim 20 is directed to a genus of polypeptide comprising "a purified ULIP polypeptide" selected from the group consisting of a polypeptide comprising SEQ ID NO: 8, "a derivative" of a polypeptide comprising SEQ ID NO: 8, and a "biological active polypeptide" of a polypeptide comprising SEQ ID NO: 8.

The term "derivative" is defined in the specification at page 5, line 30, through page 6, line 7. A "derivative" is any variant polypeptide of the polypeptide SEQ ID NO: 8 or any other molecule resulting from the genetic and/or chemical modification of the polypeptide of SEQ ID NO: 8, an isoform thereof (including the polypeptides of SEQ ID NO: 2, SEQ ID NO: 4, and SEQ ID NO: 6), a fragment thereof, or a modification thereof. The specification teaches the derivatives generally have at least one of the biologically activities or properties selected from the group consisting of inducing neuronal development, controlling neuronal development, and antigenicity.

Given the broadest, reasonable interpretation of the claims, without reading limitations into the claims from the disclosure, the "derivatives" are molecules that vary in function; notably, the claims do not expressly recite the derivative is able to bind anti-CV2 antibodies. Claim 14, for example, merely recites that the polypeptide is optionally

attached to a support under conditions allowing the formation of specific immunological complexes between the polypeptide and the autoantibodies present optionally present in the sample; the autoantibodies optionally present in the sample are not necessarily anti-CV2 antibodies. Moreover, the derivatives are not described by the claims as having any particularly identifying functional or structural features and, more particularly, no one structural feature that correlates with any one functional feature. Accordingly, the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the genus of "derivatives" to which the claims are directed. Therefore, the written description of the claimed invention would not be sufficient to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Further regarding claim 20, which is directed to a genus of polypeptide comprising a "biological active polypeptide fragment" of a polypeptide comprising SEQ ID NO: 8, again, the claim does not expressly recite the polypeptide binds anti-CV2 antibodies. The term "biologically active" is defined in the specification, as "having properties of induction and/or control of neuronal development and/or antigenic properties" (page 6, lines 8-10). Thus, the polypeptide comprising a biological active polypeptide fragment of a polypeptide comprising SEQ ID NO: 8 is not necessarily able to bind anti-CV2 antibodies; the claim merely recites that the contacting step is carried out under conditions sufficient to allow the formation of specific immunlogical complexes between the peptide and antibodies (not necessarily anti-CV2 antibodies) present in the sample. Although the members of the genus of such polypeptides comprise a fragment of SEQ ID NO: 8, their structures can vary markedly. Furthermore, their functions, which can also vary markedly, have not been described in such detail that the skilled artisan could immediately envision, recognize or distinguish at least a substantial number of these polypeptides, especially since there is no disclosed correlation between any particularly identifying, common structural feature and a specific function, which is also common to the polypeptides.

Claims 30-32 are drawn to a genus of reagents comprising a solid support and "a peptide comprising an antigenic portion" of a polypeptide comprising SEQ ID NO: 8.

The claimed reagents do not necessarily comprise a polypeptide comprising SEQ ID NO: 8, nor do the reagents necessarily consist of a fragment of a polypeptide comprising SEQ ID NO: 8. Because the reagents merely comprise an antigenic portion of a polypeptide comprising SEQ ID NO: 8, the genus of reagents encompasses reagents comprising peptides that differ markedly in both structure and function, since the peptides do not necessarily have the same substantial structure as the polypeptide of SEQ ID NO: 8 nor its function. Moreover, the members of the genus of reagents only share a common antigenic portion, but this antigenic portion is not disclosed as a particularly identifying feature of the peptides of which the reagents are comprised, nor is its structural presence correlated with any particularly identifying functional attribute shared by most of the peptides. Thus, a reagent comprising a polypeptide of SEQ ID NO: 8 is not deemed representative of at least most of the members of the claimed genus of reagents comprising a peptide.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by

Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

17. Claims 10, 14, 15, 20, 22, 27, and 33-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a polypeptide comprising the amino acid sequence of SEQ ID NO: 8, or a fragment thereof, which polypeptide binds anti-CV2 antibodies, or a kit comprising said polypeptide, to detect the presence of anti-CV2 antibodies in a biological sample, does not reasonably provide enablement for making and using a derivative of the polypeptide of SEQ ID NO: 8 to detect the presence of anti-CV2 antibodies in a biological sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 10 is drawn to a method for detecting the presence of anti-CV2 antibodies in a biological sample. Claim 14 is drawn to a method for diagnosing a paraneoplastic neurological syndrome and the early diagnosis of a tumor associated therewith in a subject, whereas claim is 20 is drawn to a method for diagnosing a paraneoplastic syndrome, in either case by a process comprising detecting the presence of anti-CV2 antibodies in a biological sample taken from the subject. Claim 15 is drawn to a kit for diagnosing paraneoplastic neurological syndromes and early diagnosis of tumors associated therewith, which comprises reagents for detecting anti-CV2 antibodies in a biological sample taken from the subject. Claim 22 is drawn to the method of claim 20, wherein the polypeptide is an antigenic fragment of a polypeptide comprising SEQ ID NO: 8. Despite the issue under 35 USC §112, second paragraph, set forth below, claim 27 is herein drawn to the method of claim 25, wherein the polypeptide is an antigenic fragment of a polypeptide comprising SEQ ID NO: 8. Claims 33-35 are drawn to a diagnostic kit.

Claims 10, 14, 15, 20, and 33-35 are directed to a genus of "derivatives" of a ULIP polypeptide comprising SEQ ID NO: 8.

As noted above, given the broadest, reasonable interpretation of the claims, without reading limitations into the claims from the disclosure, the "derivatives" are not necessarily able to bind anti-CV2 antibodies.

However, only derivatives that bind anti-CV2 antibodies can be used to detect the presence of such antibodies in a biological sample.

In addition, the specification fails to teach how derivatives of the polypeptide of SEQ ID NO: 8, which do not bind anti-CV2 antibodies, can be used to detect anti-CV2 antibodies in a biological sample and how such derivatives might be useful in diagnosing a paraneoplastic syndrome and the early diagnosis of a tumor associated therewith in a subject. The only means for detecting the presence of anti-CV2 antibodies disclosed is the detection of an immune complex that forms between the polypeptide of SEQ ID NO: 8 or an antigenic fragment thereof that binds anti-CV2 antibodies and the antibodies present in a biological sample; and the only method for diagnosing a paraneoplastic syndrome and a tumor associated therewith in a subject, which is disclosed, is one comprising detecting by such means, the presence of anti-CV2 antibodies in biological samples taken from subjects. Elaborating other means for detecting anti-CV2 antibodies and thereby rendering a diagnosis using a derivative of a polypeptide comprising SEQ ID NO: 8, which does not bind anti-CV2 antibodies, would entail an undue amount of additional experimentation.

Furthermore, the derivatives are, by definition, any variant polypeptide of the polypeptide SEQ ID NO: 8 or any other molecule resulting from the genetic and/or chemical modification of the polypeptide of SEQ ID NO: 8, an isoform thereof, or a fragment thereof; see the specification at page 5, line 30, through page 6, line 7. Accordingly, the derivatives to which the claims are directed vary markedly in structure.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence

or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Only the polypeptide of SEQ ID NO: 8 and antigenic fragments thereof that bind to anti-CV2 antibodies could be readily be made and used without having to perform an undue amount of additional, non-routine experimentation. The specification, therefore, fails to provide an amount of guidance, direction, and exemplification, which is reasonably commensurate in scope with the claims.

For example, the specification fails to teach how derivatives of SEQ ID NO: 8 can be made, and then used to detect anti-CV2 antibodies, by altering the amino acid sequence of SEQ ID NO: 8 without adversely affecting the ability of the resultant derivative to bind to the antibodies. The specification does not teach which amino acid residues are contacted by anti-CV2 antibodies, nor does it teach by which other amino acid residues these critical amino acid residues can be replaced without loss of the binding activity.

As evidenced by Greenspan et al. (*Nature Biotechnology* **7**: 936-937, 1999), defining an epitope of an antigen to which an antibody binds is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destablilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. The epitope to which any given antibody binds can only be identified empirically. Anti-CV2 antibodies may recognize multiple epitopes. Accordingly, the skilled artisan could not determine which amino acids of the polypeptide of SEQ ID NO: 8 are critical or essential to the binding of anti-CV2 antibodies without first having to perform an undue amount of additional experimentation.

Further additional, non-routine experimentation would then be necessary to determine other amino acid residues that can replace the critical amino acids of the epitopes to which the anti-CV2 antibodies bind without loss of the resultant derivatives ability to bind anti-CV2 antibodies, since the skilled artisan cannot reliably and accurately predict the consequence of amino acid substitutions. Burgess et al. (*Journal of Cell Biology* **111**: 2129-2138, 1990) exemplifies the sensitivity of proteins to alterations of even a single amino acid. Burgess et al. teaches that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. As another example, Lazar et al. (*Molecular and Cellular Biology*, 1988, **8**: 1247-1252) teaches that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. Thus, even a single conservative type amino acid substitution may adversely affect the function of a protein.

The specification teaches some variants of the polypeptide of SEQ ID NO: 8, including the ULIP-1, ULIP-2, and ULIP-3; however, the specification also teaches that samples of serum containing anti-CV2 antibodies, which bind to the polypeptide of SEQ ID NO: 8, do not predictably and consistently bind to these variants; see, e.g., page 36, lines 9-27; and page 37, Table 1. Accordingly, the results disclosed in the specification support the present assertion that the skilled artisan cannot practice the claimed invention without the need to first perform an undue amount of additional experimentation, since the skilled artisan cannot predict which derivatives (e.g., variants) of the polypeptide of SEQ ID NO: 8 bind anti-CV2 antibodies.

Claims 22 and 27 are drawn to methods comprising detecting anti-CV2 antibodies in a biological sample acquired from a subject using a polypeptide that is an antigenic fragment of a polypeptide of SEQ ID NO: 8. The polypeptide recited in claims 22 and 27 is not, however, limited to a polypeptide that binds anti-CV2 antibodies. Unless the polypeptide binds anti-CV2 antibodies, one could not detect their presence; and the specification does not teach whether the presence of other antibodies that may

be present in the biological sample, which bind a polypeptide recited in claims 22 and 27, are indicative of a paraneoplastic syndrome or a tumor.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation.

18. Claims 9, 14, 15, 20-22, 24, 25, 27, 29, and 33-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using the polypeptide of SEQ ID NO: 8 or a fragment of the polypeptide of SEQ ID NO: 8 that binds anti-CV2 antibodies, or a kit comprising said polypeptide or fragment, to detect the presence of anti-CV2 antibodies in a biological sample taken from a subject and to thereby diagnose a paraneoplastic neurological syndrome selected from the group consisting of cerebellar ataxia, sensory motor neuropathy, uveitis and retinopathy, limbic encephalitis, myasthenia gravis, encephalopathy, frontal dementia, loss of vision, and Lambert-Eaton myasthenic syndrome, which is associated with the presence of a tumor selected from the group consisting of undifferentiated mediastinal carcinoma, malignant lymphoepithelial thymoma, small cell lung carcinoma, uterine sarcoma, and cervix uterus sarcoma in the subject, does not reasonably provide enablement for making and using the polypeptide of SEQ ID NO: 8 or a fragment of the polypeptide of SEQ ID NO: 8 that binds anti-CV2 antibodies, or a kit comprising said polypeptide or fragment, to detect the presence of anti-CV2 antibodies in a biological sample taken from a subject and to thereby diagnose any paraneoplastic neurological syndromes and/or any tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 9 is drawn to a composition for diagnosing a paraneoplastic neurological syndrome and tumor in which anti-CV2 antibodies are expressed. Claims 14 and 15

are drawn to a method and a kit, respectively, for diagnosing a paraneoplastic neurological syndrome and tumor in which anti-CV2 antibodies are expressed. Claims 20-22 and 24 are drawn to methods for diagnosing a paraneoplastic (not necessarily neurological) syndrome. Claims 25 and 29 are drawn to methods for diagnosing a tumor that elicits an autoimmune response in a subject that results in the subject expressing anti-CV2 antibodies. Claims 33-35 are drawn to a diagnostic kit.

As an initial matter, claim 9 is drawn to a composition for diagnosing a paraneoplastic neurological syndrome and tumor in which anti-CV2 antibodies are expressed, whereas claims 14 and 15 are drawn to a method for diagnosing a paraneoplastic neurological syndrome and tumor in which anti-CV2 antibodies are expressed. However, most, if not all, tumors do not express antibodies, or more particularly anti-CV2 antibodies. Of the many different types of tumors, only certain lymphomas produce antibodies, but there is no factual evidence of record that lymphomas express anti-CV2 antibodies and the claims are not limited to compositions and methods for diagnosing lymphoma. Nonetheless, as noted above, it is recognized that the invention is disclosed as useful in diagnosing paraneoplastic neurological syndromes in which autoimmune-associated anti-CV2 antibodies are present in the serum or cerebrospinal fluid of patients with certain tumors, not in diagnosing tumors that express anti-CV2 antibodies.

Claims 33-35 are drawn to a diagnostic kit; however, the specification only provides guidance and direction for using such a kit to diagnose paraneoplastic neurological syndromes in which anti-CV2 antibodies are present a biological sample (e.g., blood or cerebrospinal fluid) of the subject and tumors associated therewith. The specification provides no indication that a kit comprising an antigenic portion of a polypeptide comprising SEQ ID NO: 8 or a derivative thereof can be used to diagnose any other disease or disorder, including paraneoplastic syndromes that are not neuropathic.

To the extent that claims 9, 14, 15, 20-22, 24, 25, 27, 29, and 33-35 are drawn to a composition, kit, or methods for diagnosing a paraneoplastic syndrome, including or limited to a paraneoplastic neuropathy, and an associated tumor that elicits an

autoimmune response in a subject that results in the subject expressing anti-CV2 antibodies, the amount of guidance, direction, and exemplification disclosed would not be sufficient to enable the skilled artisan to use the claimed invention without the need to first perform an undue amount of additional experimentation. The skilled artisan cannot predict which paraneoplastic syndromes, including paraneoplastic neuropathies, are, or can be characterized by the presence of anti-CV2 antibodies in a biological sample (e.g., blood or cerebrospinal fluid) of a subject, apart from those that are disclosed as so; nor can the skilled artisan predict which tumors associated with such paraneoplastic syndromes will elicit the production of anti-CV2 antibodies, apart from those that are disclosed as able to do so.

Rogemond et al. (*Clin. Rev. Allergy Immunol.* 2000 Aug; **19** (1): 51-59) reviews the association of anti-CV2 antibodies and paraneoplastic neurological syndromes and teaches: "Anti-CV2 antibodies have only been found in patients in whom there was a close relationship between neurological syndromes and tumor" (page 58, paragraph 2). Anti-CV2 autoantibodies are apparently not produced in a subject in the absence of tumors that express POP-66/ULIP-4, as normally the polypeptide is predominantly expressed only during early development and otherwise in a very limited manner in the adult brain; see the specification at page 4, lines 6-19.

The specification teaches that of eight glioblastomas, four expressed the messenger RNA (mRNA) encoding the polypeptide of SEQ ID NO: 8 (i.e., POP-66/ULIP-4); see the specification at page 40, lines 5 and 6. However, the specification also teaches none of ten oligodendrogliomas expressed the mRNA encoding ULIP-4. Therefore, it is evident, given the teachings set forth in the specification, that the skilled artisan cannot predict whether any given tumor expresses the mRNA encoding the polypeptide of SEQ ID NO: 8.

Only tumors that express the mRNA encoding the polypeptide of SEQ ID NO: 8 might be expected to elicit the production of anti-CV2 antibodies, since anti-CV2 antibodies are disclosed as autoantibodies against the polypeptide of SEQ ID NO: 8; see, e.g., page 2, line 36, through page 5, line 14.

However, although the specification teaches that POP-66/ULIP-4 is expressed by glioblastomas, the specification fails to teach whether anti-CV2 antibodies are present in the cerebrospinal fluid or blood of subjects diagnosed with glioblastoma. As of yet, there appear to be no reports in the relevant scientific literature that glioblastoma is associated with the production of anti-CV2 antibodies. Because normal brain cells expressing POP-66/ULIP-4 do not cause the production of anti-CV2 antibodies, however, it seems unlikely that glioblastoma will be found to be associated with the presence of the antibodies. Moreover, because the polypeptide is normally expressed in certain cells of the adult brain and anti-CV2 antibodies are not normally present in the blood or serum of individuals, unless the individual has a tumor that arose from a tissue other than of the brain, there is no factual evidence that the glioblastomas result, directly or indirectly, in the production of anti-CV2 antibodies. Therefore, because it is not known whether glioblastomas are associated with the presence of anti-CV2 antibodies, the skilled artisan could not use the claimed inventions to diagnose glioblastomas and associated paraneoplastic neuropathies without first performing an undue amount of additional experimentation to determine whether the invention can be used with such purpose.

Because the skilled artisan cannot predict which tumors express the polypeptide of SEQ ID NO: 8, and moreover cannot predict which of those are associated with the presence of anti-CV2 antibodies produced against this polypeptide, the skilled artisan could only use the claimed inventions without the need to perform an undue amount of additional experimentation to diagnose tumors that are disclosed as eliciting, directly or indirectly, the production of anti-CV2 autoantibodies against the polypeptide.

The specification teaches that serum samples acquired from patients diagnosed with paraneoplastic cerebellar degeneration, paraneoplastic uveitis and an undifferentiated carcinoma, paraneoplastic limbic encephalitis and thymoma, paraneoplastic encephalomyelitis and small cell lung cancer, paraneoplastic cerebellar degeneration and uterine sarcoma, paraneoplastic limbic encephalitis, neuropathy and small cell lung cancer contained anti-CV2 antibodies that reacted with POP-66/ULIP-4; see, e.g., page 37, Table 1. Notably, however, the specification does not appear to

teach with what type of undifferentiated carcinoma the patient from whom serum sample no. 90-002 was diagnosed, but there are notably several different types of undifferentiated carcinomas, since carcinomas arise from the epithelium, found in skin or more commonly in the lining of body organs (e.g., breast, lung, stomach, bowel, prostate).

The prior art teaches that the presence of anti-CV2 antibodies in patients is associated with various paraneoplastic neuropathies, including cerebellar ataxia, sensory motor neuropathy, uveitis and retinopathy, limbic encephalitis, myasthenia gravis, encephalopathy, frontal dementia, loss of vision, and Lambert-Eaton myasthenic syndrome in patients diagnosed with various tumors, including undifferentiated mediastinal carcinoma, malignant lymphoepithelial thymoma, small cell lung carcinoma, uterine sarcoma, and cervix uterus sarcoma; see, e.g., Honnorat et al. (*J. Neurol. Neurosurg. Psychiatry.* 1996; **61**: 270-278) (of record), particularly the abstract and table at page 272.

At page 40 (lines 12-19), the specification discloses that the polypeptide could be expressed in tumors of the breast and ovary, but the specification provides no factual evidence to support this assertion. In light of the disclosure that glioblastomas express the protein, while oligodendrogliomas do not, it is evident that the skilled artisan cannot reliably and accurately predict whether breast and ovarian tumors express the polypeptide and are associated with the presence of anti-CV2 antibodies in the blood or cerebrospinal fluid of patients having such tumors. The determination of whether such tumors express the polypeptide and are associated with the presence of anti-CV2 antibodies can only be made empirically.

At page 5 (lines 7-14), the specification discloses that the proteins of the ULIP family, which includes POP-66/ULIP-4, could play a role in any other form of cancer not associated with paraneoplastic neurological syndromes. However, the specification provides no factual evidence to support this assertion, since apparently only serum samples acquired from patients diagnosed with paraneoplastic neurological syndromes were studied to determine the presence of anti-CV 2 antibodies; see, e.g., page 37, Table 1. Furthermore, Honnorat et al. (cited *supra*) teaches anti-CV2 antibodies seem

to be mainly associated with small cell lung cancer, although they also occur in cases of uterine sarcoma or malignant thymoma, and a range of neurological syndromes, *all of which are known to be paraneoplastic* (page 277, column 2). Indeed, the prior art does not suggest that forms of cancer not associated with paraneoplastic neurological syndromes might be diagnosed by detecting the presence of anti-CV2 antibodies in the blood or cerebrospinal fluid of patients.

After the effective filing date sought by Applicant in this instance, Antoine et al. (*J. Neurol. Neurosurg. Psychiatry.* 1999; **67**: 7-14) teaches that not all carcinoma associated with paraneoplastic peripheral neuropathies are characterized by the presence of autoantibodies, or more particularly by the presence of anti-CV2 antibodies; see entire document (e.g., the abstract). Only one of seven patients with paraneoplastic neurological syndromes had anti-CV2 antibodies, whereas the other six had anti-Hu antibodies (page 9, Table 1). Thus, Antoine et al. teaches some carcinomas associated with paraneoplastic peripheral neuropathies are characterized by the presence of anti-Hu antibodies, but not by the presence of anti-CV2 antibodies; see, e.g., the abstract. Antoine et al. teaches still other carcinomas were not associated with the presence of any of the autoantibodies assayed, including anti-CV2 antibodies, despite manifestation of paraneoplastic neuropathies (abstract). Again, Rogemond et al. (cited *supra*) teaches that anti-CV2 antibodies have only been found in patients in whom there was a close relationship between neurological syndromes and tumor.

Accordingly, in view of the instant disclosure, the prior art, and the teachings of Antoine et al. (cited *supra*), it is evident that one skilled in the art cannot predict which tumors associated with neuropathies are characterized by the expression of the polypeptide of SEQ ID NO: 8 or by the presence of anti-CV2 antibodies. Therefore, absent specific teachings of which tumors express the polypeptide and can be diagnosed by detecting the presence of anti-CV2 antibodies, and particularly tumors that are not associated with neuropathy, the skilled artisan could not use the claimed invention without having to first perform an undue amount of additional experimentation.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230

USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation.

19. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using an isolated host cell transfected with a vector according to claim 6, does not reasonably provide enablement for any host cell transfected with a vector according to claim 6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 7 is drawn to a host cell transfected with a vector according to claim 6. The claim is broadly interpreted to encompass host cells, which are not isolated and are comprised within an organism. Thus, the claims encompass host cells that have been transfected with a vector according to claim 6 that are comprised within an animal, including nonhuman or human animals, treated using gene therapy.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification set forth therein would not be sufficient to enable the skilled artisan to make and use the claimed invention without the need to perform additional, and an undue amount of experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The specification discloses that nucleic acid molecules and vectors encoding the human polypeptide of SEQ ID NO: 8 (i.e., ULIP-4) can be used to produce medicaments and pharmaceutical compositions, which can be administered to patients

to treat diseases by gene therapy; see, e.g., page 8, lines 14-22; page 13, lines 22-31; page 14, lines 21-26; and page 15, lines 12-34. Furthermore, the specification contemplates transgenic animals that express the human polypeptide; see page 41, lines 16 and 17. The specification exemplifies the production of transgenic animals expressing the human polypeptide of SEQ ID NO: 8 (i.e., ULIP-4) by teaching the production of transformed fruit flies; see pages 41 and 42, Example 13.

The specification does not provide a sufficient amount of guidance, direction, or exemplification to enable the skilled artisan to make or use host cells that are comprised within a non-human transgenic animal, since a fruit fly is not an animal but an insect. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predictable; nor is the transgenic embryo always viable. Houdebine (*Journal of Biotechnology* 1994, 34: 269-287) teaches the vectors to be used for directing the expression of transgenes in any given tissue, or in all tissues, must contain the appropriate regulatory regions; see entire document (e.g., paragraph bridging pages 272 and 273). Houdebine teaches expression is heavily dependent on the site of integration in the host genome and the site of integration is presently unpredictable (page 27, column 1). Therefore, it is concluded that one of skill in the art would need to perform an undue amount of experimentation in order to make and use the claimed host cell comprised within a transgenic animal.

In addition, the specification does not teach provide a sufficient amount of guidance, direction, and exemplification to enable the skilled artisan to have a reasonable expectation of successfully producing the claimed host cells within a living organism by gene transfer, or *gene therapy*. The art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the specification does not remedy and would preclude the skilled artisan from having a reasonable expectation of successfully making and using the claimed invention without need of performing an undue amount of experimentation.

For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, **389**: 239-242) teaches that the Achilles heel of gene therapy is gene delivery (page 239, column 3). Verma et al. states that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression; see entire document (e.g., page 239, column 3). Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, **2**: 111-133) teaches that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies; see entire document (e.g., page 111, column 2). In addition, Amalfitano et al. discusses numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teaches the use of adenoviral vectors can be ineffective because of the induction of strong immune responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself; see entire document (e.g., abstract).

It is noted that Amalfitano et al. teaches that a despite general lack of success, the first conclusive evidence that gene therapy can show efficacy in humans was achieved in human X-linked SCID subjects *via* retrovirus transduction (page 111, column 2). However, since the publication, The Department of Health and Human Services has released a memorandum dated January 14, 2003, a copy of which is attached to this Office action, that urges all such investigations to be discontinued until new data are available, the possible etiology and risks of adverse events associated are considered, and recommendations emerge. Despite the initial promise of the trial studying gene transfer as a possible treatment for the disease, investigators have found that retroviral-mediated insertion of the transgene has caused the subjects to develop cancer. The results of the trial underscore the high degree of unpredictability associated with the art and the fact that the skilled artisan could not make or use the claimed invention with a reasonable expectation of success without need to perform additional and an undue amount of experimentation.

The state of the art, as a whole, is well defined by Pandha et al. (*Current Opinion in Investigational Drugs* 2000; **1** (1): 122-134). Pandha et al. teaches:

> Despite the rapid technological advances that continue to sustain the field of cancer gene therapy, few individual patients have benefited from the revolution so far. The plethora of clinical trials described confirms that each malignancy will have its own ideal strategy

> based on the associated molecular defects, and there has been rapid progress from this viewpoint. At the same time, there has been a renewed appreciation for the limitations to gene therapy, which include low efficiency of gene transfer, poor specificity of response and methods to accurately evaluate responses, and lack of truly tumor-specific targets at which to aim. As with all new therapies, we are climbing a steep learning curve in terms of encountering treatment-related toxicities, as well as profound ethical and regulatory issues (abstract).

In view of the preponderance of evidence establishing the state of the art, now and at the time the application was filed, and the level of unpredictability associated therewith, in the absence of a disclosure of an amount of guidance, direction, and exemplification that is reasonably commensurate in scope with the claims, it appears that skilled artisan could not make and use the claimed invention with a reasonable expectation of success without having the need to perform an undue amount of experimentation.

This issue can be remedied by amending claim 7 to recite "isolated" before "host cell".

20. Claims 14, 15, 27, and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is indefinite because the claim recites the limitation, "the blood sample". The claim lacks an antecedent basis for the recitation of this limitation in line 8, because the term "blood" was deleted from preceding line 4.

Claim 15 is indefinite because the claim recites the limitation, "the purified ULIP polypeptide, derivative or polypeptide fragment". The claim lacks an antecedent basis for the recitation of this limitation in lines 8 and 9, because the term "biologically active fragment" was deleted from preceding line 5.

Claim 27 is indefinite because the claim recites, "wherein the polypeptide is an antigenic fragment of a polypeptide comprising amino acid sequence SEQ ID No. 8", but depends from claim 25, which recites that the polypeptide comprises the amino acid sequence of SEQ ID NO: 8. The polypeptide of claim 27 cannot be a polypeptide comprising SEQ ID NO: 8 and also an antigenic fragment of a polypeptide comprising

SEQ ID NO: 8, because, by definition, a fragment of a polypeptide is only a portion of the polypeptide, which will not comprise the entirety of the amino acid sequence of the polypeptide. Accordingly, the metes and bounds of the subject matter that Applicant regards as the invention cannot be determined.

Claim 34 is indefinite because the claim recites the limitation, "said polypeptide-antibody complexes". The claim lacks an antecedent basis for the recitation of this limitation, because the term "polypeptide-antibody complexes" is not recited in claim 33.

Claim Rejections - 35 USC § 102

21. Claims 1, 9, 10, 14, 20, 21, 24, 25, and 29-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Honnorat et al. (*J. Neurol. Neurosurg. Psych.* 1996; **61**: 270-278) (of record), as evidenced by Honnorat et al. (*Eur. J. Neurosci.* 1999 Dec; **11** (12): 4226-4232).

Claim 1 is drawn to a purified polypeptide comprising the amino acid sequence of SEQ ID NO: 8; whereas claim 9 is drawn to a composition comprising a purified polypeptide comprising the amino acid sequence of SEQ ID NO: 8. Claims 10 and 14 are drawn to a method for detecting the presence of anti-CV2 antibodies in a biological sample taken from an individual comprising contacting a biological sample with a polypeptide comprising the amino acid sequence of SEQ ID NO: 8 and detecting any immunological complex that forms between anti-CV2 antibodies present in the sample and the polypeptide. Claims 20, 21, 24, 25, and 29 are drawn to a method for diagnosing a paraneoplastic syndrome or a tumor that elicits the production of anti-CV2 antibodies in a subject by detecting the presence of anti-CV2 antibodies in a sample taken from the subject by a process comprising contacting a biological sample with a polypeptide comprising the amino acid sequence of SEQ ID NO: 8 and detecting any immunological complex that forms between anti-CV2 antibodies present in the sample and the polypeptide. Claims 30-32 are drawn to a reagent comprising a solid support and a peptide comprising an antigenic portion of a polypeptide comprising the amino acid sequence of SEQ ID NO: 8, wherein said solid support comprises animal brain of

which the polypeptide is endogenous or wherein the antigenic portion is attached to the solid support.

Honnorat et al. (1996) teaches a composition comprising a purified polypeptide that is 66 kDa, which is produced by human brain cells and binds anti-CV2 antibodies; see entire document (e.g., the abstract; page 271, column 2; page 274, column 2; and page 276, Figure 7). In addition, Honnorat et al. teaches a Western blot (i.e., a solid membrane) to which the purified 66 kDa polypeptide is attached; see, e.g., page 276, Figure 7. Honnorat et al. teaches that contacting the purified polypeptide affixed to the Western blot with serum samples indicates the presence of anti-CV2 antibodies in the serum samples taken from individuals; see, e.g., page 276, Figure 7. Honnorat et al. teaches that the detection of anti-CV2 antibodies in patients with paraneoplastic neurological disorders should be considered an indication of the presence of an occult cancer in the patient (abstract). Furthermore, Honnorat et al. teaches fixed tissue sections of both rat and human brain comprise a polypeptide that is recognized by anti-CV2 antibodies, which bind the 66 kDa polypeptide endogenous to human brain cells; see, e.g., page 276, Figures 6 and 7.

As evidenced by Honnorat et al. (1999), the 66 kDa polypeptide of Honnorat et al. (1996), which is endogenous to human brain cells, and to which anti-CV2 antibodies bind, is a polypeptide that comprises an amino acid sequence that is identical to SEQ ID NO: 8; see entire document (e.g., the abstract; page 4230, Figure 5).

22. Claims 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Antoine et al. (*J. Neurol. Sci.* 1993 Jul; **117** (1-2): 215-223) (of record), as evidenced by Honnorat et al. (*Eur. J. Neurosci.* 1999 Dec; **11** (12): 4226-4232).

Claims 30-32 are drawn to a reagent comprising a solid support and a peptide comprising an antigenic portion of a polypeptide comprising the amino acid sequence of SEQ ID NO: 8 (claim 30), wherein said support comprises animal brain and said antigenic portion of the polypeptide is endogenous to the brain (claim 31) or wherein said antigenic portion is attached to the support (claim 32). The claims read on a fixed section of brain tissue comprising cells that express an endogenous polypeptide

comprising SEQ ID NO: 8. The polypeptide, and therefore the antigenic portion of which the polypeptide is comprised, is "attached" to the brain tissue during fixation.

Antoine et al. teaches fixed sections of human brain; see entire document (e.g., page 217, "*Immunocytochemistry*").

As evidenced by Honnorat et al., fixed sections of human brain comprise an endogenous 66 kDa polypeptide, which comprises the amino acid sequence set forth as SEQ ID NO: 8, to which anti-CV2 antibodies bind; see entire document (e.g., the abstract; page 4230, Figure 5).

At pages 5 and 6 of the amendment filed October 9, 2003, Applicant has traversed the similar ground of rejection set forth in section 23 of the previous Office action mailed April 9, 2003, arguing that the prior art does not anticipate the claimed invention because Antoine et al. merely describes that anti-CV2 antibodies react with 66 kDa proteins without specifically disclosing that the 66 kDa protein is a polypeptide comprising SEQ ID NO: 8.

As Applicant's arguments are relevant to the instant ground of rejection, Applicant's arguments have been carefully considered, but have not been found persuasive for the following reasons:

Antoine et al. teaches fixed sections of human brain. Although Applicant has argued that Antoine et al. does not disclose that the 66 kDa polypeptide of which human brain cells are comprised, and to which anti-CV2 antibodies bind, is the polypeptide of SEQ ID NO: 8, as evidenced by Honnorat et al., fixed sections of human brain comprise an endogenous 66 kDa polypeptide, which comprises the amino acid sequence set forth as SEQ ID NO: 8; see entire document (e.g., the abstract; page 4230, Figure 5). Accordingly, absent a showing of any difference, the fixed sections of human brain disclosed by the prior art are deemed the same as the claimed reagent.

Claim Rejections - 35 USC § 103

23. Claims 10, 15, and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamajima et al. (*Gene.* 1996; **180**: 157-163) (or record) in view of Thompson et al. (*Biotechniques*. 1992 May; **12** (5): 656-658).

Claim 10 is drawn to a method comprising contacting a biological sample with a polypeptide comprising SEQ ID NO: 8, a derivative of a polypeptide comprising SEQ ID NO: 8, or a fragment of a polypeptide comprising SEQ ID NO: 8 that binds to anti-CV2 antibodies and detecting any specific immunological complexes optionally formed. Although the "derivative" does not necessarily bind "anti-CV2 antibodies", since any specific immunological complexes formed following the step of contacting the biological sample with the derivative indicates the presence of "anti-CV2 antibodies", the antibodies of which the specific immunological complexes are formed are deemed the same as "anti-CV2 antibodies".

The specification defines the term "derivative", in the context of the claims, as any variant polypeptide of the polypeptide of SEQ ID NO: 8 or any other molecule resulting from a modification of genetic and/or chemical nature of the amino acid sequence of SEQ ID NO: 8, which is obtained by mutation, deletion, addition, substitution, and/or chemical modification of a single or limited number of amino acids of SEQ ID NO: 8 or any isoform sequence, which is identical to SEQ ID NO: 2, SEQ ID NO: 4, or SEQ ID NO: 6, a fragment thereof, or a modification thereof containing one or more amino acids in the D-enantiomer form, provided that isoform or modification retain at least one biological activity of the polypeptide of SEQ ID NO: 8, including its ability to induce or control neuronal development and its antigenicity; see page 5, line 32, through page 6, line 10.

Claim 10 thus reads on a method comprising, for example, detecting a derivative of a polypeptide comprising SEQ ID NO: 8 (i.e., a variant of the polypeptide of SEQ ID NO: 8) by contacting the derivative blotted to a membrane with a biological sample containing an antibody that binds the derivative and detecting the immune complexes formed between the derivative and the antibody, whereby the presence of such an immune complex indicates the presence of the antibody in the biological sample. In the vernacular of the art, such assays are commonly referred to Western blot analyses.

Claim 15 is drawn to a kit comprising a purified polypeptide comprising SEQ ID NO: 8 or a derivative of a polypeptide comprising SEQ ID NO: 8 and means of visualization of the formation of specific immune complexes between an anti-POP-66

auto-antibody and the purified polypeptide and/or means of characterizing such complexes. As explained above, by definition, claim 15 reads on a kit comprising a purified variant of the polypeptide of SEQ ID NO: 8. Such a variant polypeptide is, itself, a means of visualizing the formation of a specific immune complex formed of an antibody that binds the variant polypeptide and the polypeptide.

Claims 33-35 are drawn to a kit comprising an antigenic portion of a polypeptide comprising SEQ ID NO: 8 or a derivative of a polypeptide comprising SEQ ID NO: 8 (claim 33), which kit further comprises means for visualizing formation of polypeptide-antibody complexes (clam 34) or wherein the antigenic portion is purified (claim 35). Again, given the disclosed definition of the term "derivative", the claims read a kit comprising a purified variant of the polypeptide of SEQ ID NO: 8.

Hamajima et al. teaches the amino acid sequences of four polypeptides, which are each, by definition, derivatives of a polypeptide comprising SEQ ID NO: 8, since each of the polypeptides is a variant of the polypeptide of SEQ ID NO: 8; see entire document (e.g., the abstract and page 160, Figure 1).

However, Hamajima et al. does not expressly teach producing or purifying any of the disclosed polypeptides or using any one of the polypeptides in a process comprising contacting a biological sample with the polypeptide and detecting specific immune complexes formed of the polypeptide and an antibody that binds the polypeptide, which is contained in the biological sample (e.g., Western blot analysis) (claim 10).

Furthermore, Hamajima et al. does not expressly teach a kit comprising any of the disclosed polypeptides, which further comprises a means for visualizing an immune complex of the polypeptide and an antibody that binds the polypeptide (claims 15 and 33-35).

Thompson et al. teaches a general method for the electrophoretic transfer of proteins from stained gels to membranes and subsequent Western detection of specific proteins on the stained membranes; see entire document (e.g., the abstract). Thompson et al. that proteins are separated by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE) and the gels are stained using either of two different methods followed by electrophoretic transfer to nitrocellulose membranes, for example (abstract).

Thompson et al. teaches the transferred proteins, which are thus attached to the membranes, can be detected by contacting the proteins with an antibody that binds the protein of interest. The immune complex that forms between the isolated and purified protein of interest and the antibody is then visualized.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to use any one of the polypeptides disclosed by Hamajima et al. in an assay that measures the presence of an antibody that binds the polypeptide, and which thus measures the presence of the polypeptide, by Western blot analysis, in accordance with the teachings of Thompson et al. One ordinarily skilled in the art would have been motivated at the time of the invention to do so to measure the level of, or detect the presence of either the polypeptide or the antibody that binds the polypeptide in a biological sample.

Furthermore, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to manufacture and use a kit comprising any one of the polypeptides disclosed by Hamajima et al. and any of the means disclosed by either Hamajima et al. or Thompson et al. for visualizing immune complexes formed between the polypeptide and an antibody that binds the polypeptide, which enables the methodology described by Thompson et al. One ordinarily skilled in the art at the time of the invention would have been motivated to do so because such kits could be used experimentally to detect either the polypeptide or an antibody that binds the polypeptide, kits provide greater ease, convenience, and uniformity in such experimental protocols, and kits are marketable.

24. Claims 3, 6, 7, 15, 22, 27, and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honnorat et al. (*J. Neurol. Neurosurg. Psych.* 1996; **61**: 270-278) (of record), as evidenced by Honnorat et al. (*Eur. J. Neurosci.* 1999 Dec; **11** (12): 4226-4232), in view of US Patent No. 6,455,267 B1.

Claim 3 is drawn to an isolated nucleic acid molecule that comprises a polynucleotide sequence encoding the polypeptide of SEQ ID NO: 8. Claim 6 is drawn to a cloning and/or expression vector comprising a polynucleotide sequence encoding

the polypeptide of SEQ ID NO: 8. Claim 7 is drawn to a host cell transfected with the vector of claim 6. Claim 15 is drawn to a kit comprising a polypeptide comprising SEQ ID NO: 8 or a derivative thereof and means for visualizing the formation of specific complexes between an anti-POP-66 autoantibody and the polypeptide or derivative thereof and/or means for characterizing the complexes. Claim 22 is drawn to the method of claim 20, wherein said polypeptide is an antigenic fragment of a polypeptide comprising SEQ ID NO: 8. Herein, claim 27 is drawn to the method of claim 25, wherein said polypeptide is an antigenic fragment of a polypeptide comprising SEQ ID NO: 8. Claims 33-35 are drawn to a kit comprising an antigenic portion of a polypeptide comprising SEQ ID NO: 8 or a derivative of a polypeptide comprising SEQ ID NO: 8 (claim 33), which kit further comprises means for visualizing formation of polypeptide-antibody complexes (clam 34) or wherein the antigenic portion is purified (claim 35).

As evidenced by Honnorat et al. (1999), Honnorat et al. (1996) teaches that which is set forth in the rejection above of claims 1, 9, 10, 14, 20, 21, 24, 25, and 29-32 under 35 U.S.C. 102(b).

However, Honnorat et al. (1996) does not expressly teach an isolated nucleic acid molecule comprising a polynucleotide sequence encoding the disclosed polypeptide (claim 3); nor does Honnorat et al. expressly teach a cloning and/or expression vector comprising a polynucleotide sequence encoding the polypeptide (claim 6) or a host cell transfected with such a cloning or expression vector (claim 7).

Honnorat et al. also does not expressly teach using an antigenic fragment of the polypeptide, as opposed to the entire polypeptide, for detecting anti-CV2 antibodies in a process for diagnosing paraneoplastic syndromes and tumor associated therewith (claims 22 and 27).

Finally, Honnorat et al. does not expressly teach a kit comprising the polypeptide (claim 15) or an antigenic portion thereof (claims 33-35) and a means for visualizing an immune complex that forms between the polypeptide or antigenic portion thereof and anti-CV2 antibodies (claims 15 and 34).

US Patent No. 6,455,267 B1 ('267) teaches methods for detecting the presence of autoantibodies, which is a diagnostic indication of a disease associated with such

autoantibodies; see entire document (e.g., the abstract; and column 2, lines 20-49). '267 teaches that either the intact protein to which the autoantibodies bind or an antigenic fragment thereof to which the antibodies bind can be used in the methods; see, e.g., column 3, lines 12-27. '267 teaches kits comprising the polypeptide or an antigenic fragment thereof that can be used for detecting the presence of the autoantibodies; see, e.g., column 8, line 56, through column 9, line 17. '267 teaches the kits can further comprise detectably labeled, second antibody for use in visualizing the immune complex that forms in the disclosed assays for detecting the autoantibodies (column 9, lines 5-10). '267 teaches host cells transfected with a vector comprising a polynucleotide sequence encoding the polypeptide to which the autoantibodies bind can be used to produce the polypeptide; see, e.g., column 5, lines 19-60; and column 14, lines 5-36.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to produce and use a kit comprising either the intact polypeptide disclosed by Honnorat et al. or an antigenic fragment thereof that binds anti-CV2 antibodies for use in detecting anti-CV2 antibodies and diagnosing a paraneoplastic neurological syndrome and tumor associated therewith in patients, because Honnorat et al. teaches detecting anti-CV2 antibodies is diagnostic of such disease and '267 teaches such diagnostic kits for use in detecting such autoantibodies. One ordinarily skilled in the art at the time the invention was made would have been motivate to make and use such kits to facilitate the diagnosis of a paraneoplastic neurological syndrome in which anti-CV2 antibodies are produced in patients and the tumor associated therewith.

Furthermore, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to produce a host cell transfected with a vector comprising a polynucleotide sequence encoding the polypeptide disclosed by Honnorat et al., because '267 teaches such host cells can be used to produce the polypeptide. One ordinarily skilled in the art at the time the invention was made would have been motivate to make and use such kits to facilitate the production of the polypeptide for use in making the diagnostic kits.

Conclusion

25. Claim 4 is allowed; no other claims are allowed.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
November 12, 2004

Notice to Comply	Application No.	Applicant(s)	
	09/367,496	AGUERA ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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